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Molecular docking and toxicity prediction of Δ⁹-tetrahydrocannabivarin (THCV) as antiepileptic phytocannabinoid of cannabis sativa

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Abstract

Aim: The study aims to investigate the antiepileptic effect and toxicity values of Δ⁹-Tetrahydrocannabivarin, one of the major phytocannabinoids of the Cannabis sativa plant, by in silico methods.

Material and Methods: In this study, the molecular properties of Δ⁹-Tetrahydrocannabivarin obtained from the PubChem database were investigated using the SwissADME database. The toxicity class and Lipinski parameter of Δ⁹-Tetrahydrocannabivarin were estimated by Protox II, Toxtree, and SwissADME tools, respectively. Finally, the target proteins were determined to examine the effects of Δ⁹-Tetrahydrocannabivar on epilepsy; Voltage-gated sodium channels (VGSCs/NavMs) receptor, γ-aminobutyric acid type A (GABA A) and γ-aminobutyric acid aminotransferase (GABA-AT) were obtained from the Protein Data Bank and molecular docking was performed using AutoDock Vina 1.5.7. The docking process was visualized using Discovery Studio Visualizer 2021 and LigPlot V.2.2.8 imaging programs.

Results: Cannabis sativa has low toxicity, and has good binding energy; thus, it can be a suitable candidate for epilepsy treatment.

Discussion: Although Δ⁹-Tetrahydrocannabivarin can be a suitable candidate for epilepsy treatment, in vitro and in vivo studies are needed.

Keywords

In Silico, Δ⁹-Tetrahydrocannabivarin (THCV), Molecular Docking, Toxicity Prediction, Epilepsy, Antiepileptic

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Introduction

Epilepsy is one of the most common neurological diseases affecting people of all ages, sexes, races, social classes, and geographic regions. Epilepsy is a brain disease characterized by a persistent predisposition to produce seizures and the neurobiological, cognitive, psychological, and social consequences of seizure recurrences [1]. In most cases, the disease can be diagnosed with a careful history or the observation of a seizure. Although an etiologic agent can be identified, the cause is still unknown in about half of the cases [2].

Δ⁹-Tetrahydrocannabivarin (THCV) is a cannabis-derived compound with unique properties that set it apart from the more common cannabinoid such as Δ⁹-tetrahydrocannabinol (THC). The main advantage of THCV over THC is the absence of psychoactive effects [3]. Many of the Cannabis sativa studies show that Δ⁹-Tetrahydrocannabinoid (THCV), one of the phytocannabinoids, may have an effect in the treatment of epilepsy. Δ⁹-tetrahydrocannabivarin (THCV) of Cannabis sativa has been extensively reported in the modern literature [4]. These phytocannabinoids share some similar structural features, including a dibenzopyran ring and a hydrophobic alkyl chain, but each interacts with the Endocannabinoid System (ECS) in a slightly different way [5,6]. Although each of these compounds has a slightly different molecular structure, biosynthesis, and physicochemical properties, they all interact with the ECS to maintain homeostasis and regulate lipid and glucose metabolism [7,8]. Recent studies have shown that THCV can induce seizure-like activity in rodents, act as an antagonist in the cerebellum and piriform cortical membranes, and modulate inhibitory neurotransmission at the cellular and network levels [9]. In another study, it was observed that THCV increased inhibitory neurotransmission by increasing γ-aminobutyric acid type A (GABA) release [10]. To investigate the anticonvulsant potential of Δ⁹-THCV, the effects of epileptiform activity in an in vitro piriform cortex (PC) brain slice model, cannabinoid CB1 receptor radioligand binding assays and a generalized seizure model were investigated. The results were measured using the multielectrode array (MEA) technique. It is thought that Δ⁹-THCV shows antiepileptic form and anticonvulsant properties, actions consistent with a CB1 receptor-mediated mechanism, and can be used as a possible therapeutic agent in the treatment of pathophysiological hyperexcitability states [11]. More than 33% of THCV-treated animals demonstrated complete resolution of pentylenetetrazole seizures [12]. Early preclinical studies have shown that THCV confirms that it has anticonvulsant properties.

THCV is thought to be a therapeutic agent for the treatment of epilepsy. Voltage-gated sodium channels (VGSCs / NavMs), γ-aminobutyric acid aminotransferase (GABA-AT), and γ-aminobutyric acid type A (GABA A) receptors were selected as target proteins in this study. One of the ways to increase the level of GABA in the human brain is to use small molecules that inhibit the activity of γ-aminobutyric acid aminotransferase (GABA-AT) a pyridoxal 5'-phosphate-dependent enzyme that breaks down GABA by crossing the blood-brain barrier [13,14]. Vigabatrin binds irreversibly to GABA-AT, thereby inactivating the enzyme, resulting in increased brain GABA levels to treat epilepsy, also vigabatrin is an FDA-approved drug. However, the drug has high toxicity FDA-approved, and must be used in large doses to be effective. Its irreversible binding to the enzyme poses a serious risk to the overall hemostasis of the body. Other enzyme inhibitors used in treatment include valproic acid, ethanolamine -O-sulfate (EOS), and phenelzine. Molecules such as benzodiazepines, barbiturates, carbamazepine, and others act directly on the GABA-receptor. With the production of GABA, transmembrane channels are opened and chloride or other negatively charged ions can pass through the cell, and cell stabilization is achieved. Although the compounds increase cell activity, they also decrease cell excitability [15].

This study aims to investigate the antiepileptic effects of THCV, ADMET, and its drug-like toxicity properties using in silico methods.

Material and Methods

Determination of pharmacological properties of the THCV by parameter. SwissADME. A freely accessible web-based tool (http://www.swissadme.ch) was used to help estimate absorption, distribution, metabolism, and excretion (ADME). The smile form of the THCV molecule was taken from PubChem and entered into the SwissADME web tool and obtained the results.

Toxicity assessment of the THCV.

In this study, the toxicity of THVC, such as carcinogenicity, immunotoxicity, mutagenicity and the toxicity class of THCV, oral toxicity, organ toxicity (hepatotoxicity), toxicological endpoints, toxicological pathways were evaluated, classification was carried out at different toxicity levels, as well as elucidation of possible molecular mechanisms behind toxic responses (https://tox-new.charite.de/protox_II/) [16]. The results were obtained by loading the SMILES form of the THCV molecule with Protox-II and Toxtree tools [17]. Although it is possible to manually assess compounds using the decision tree, Toxtree software has developed an automated software approach that implements the Cramer decision tree scheme [17,18] ***ADMET Lab 2.0 properties.*** Determining the biochemical processes from drug administration to elimination plays a vital role in lead optimization. An ideal drug candidate should be administered and absorbed into the systemic circulation and must be non-toxic and eliminated without affecting biological activity. ADMET properties such as absorption, distribution, metabolism, excretion, toxicity, and physicochemical properties of THCV were assessed using the online in silico prediction model ADMET lab 2.0 (https://admetmesh.scbdd.com/).

Determination of Drug-Drug Interactions. Way2Drug Software was used to determine drug-drug interaction (http://www.way2drug.com/passonline/). ***Target protein and ligand preparation.*** The three-dimensional structure of the GABA A, GABA(AT), and NAVS target proteins were taken from the RCSB PDB (https://www.rcsb.org/). Voltage-gated sodium channels (NAVMs), GABA A and GABA (AT) crystallographic structures with PDB identities (5HVX (Resolution: 2.45Å), 6X3W (Resolution: 3.30 Å), and 1OHW (Resolution: 2.30Å)), were used. Using BIOVIA Discovery Studio 2021, water molecules and bound ligand residues in the target protein were removed from the structure. The missing polar hydrogens were added to the protein. The selected ligands, energy minimization was

performed to obtain a stable conformation. Selected ligand (THCV) structure PubChem (PubChem ID: 93147) was btained from PubChem chemical compounds database (http://punchem.ncbi.nlm.nih.gov) (accessed 3.04.2023). The PyMOL V 2.0 tool was used to visualize the 3D structure of target proteins.

Molecular docking. In the study, the AutoDock Vina tool (version 1.5.7) was used to investigate the molecular interactions between target proteins and the selected ligand. Before conducting the docking analysis, the enzyme structure was optimized by removing excess ligands and water molecules using BIOVIA Discovery Studio 2021. Subsequently, all compounds were energy-optimized using the Spartan 14 (Version 1.1.4) program. Polar hydrogens were added to the protein using AutoDock Vina 1.5.7, and Kollman charges were determined. Partial charges of compounds were calculated using the Gasteiger method. Computed Surface Topography Atlas of Proteins (CASTp) software v3.0 [19] was used to identify active sites of proteins. To bind the proteins to the catalytic site, the x, y, and z coordinates were determined. For 5HVX; For x:44.966, y:69.605 z:45.874 x:78, y:60 z:66 6X3W; x:110.134, y:95.978 z:117.062 x:50, y:50 z:50 for 1OHW; x:22.58 , y:25.168 z:49.79 x:106 , y:92 z:94 and angstrom 0.375 Å. Finally, Discovery Studio molecular interactions and binding types between the selected compound and target proteins were investigated using the visualizer and LigPlot (version 2.2.8) programs [20].

Results

Pharmacological properties of THVC. In the water solubility parameter, according to the Estimated Solubility (ESOL) filter, THCV is moderately soluble, gastrointestinal (GI) is high, blood-brain barrier (BBB) is permeable, there is no substrate for Pg proteins, it is an inhibitor of enzymes other than CYP1A2 and CYP3A4, and it complies with the Lipinski rules in drug similarity, and there is no violation, as shown in Table 1.

Protox -II Web Server. Toxicity and toxicity classes of target molecules were analyzed in in silico study using a Protox -II web server. The LD50 value of the THCV molecule was found to be 482mg/kg. According to this software, it was determined that the THCV molecule belongs to the toxicity class IV according to this software and does not show high toxicity to the human body. In addition, when we look at the toxicity model report in Table 2, it is clear that THCV had an immunotoxic effect, affected Matrix metalloproteinase (MMP), which triggered the tox21 stress response pathways and affected the aryl hydrocarbon receptor (AhR) and aromatase, which triggered the tox21 nuclear signaling pathways. The results of the in silico study using the ADMET lab 2.0 web server are shown in Table 2. In this study, the parameters affecting the tox21 pathways of the molecule were examined. While PPAR-Gamma, nrf2/ARE, and p53 parameters showed inactive results according to Protox-II software, it was concluded that PPAR-Gamma was active in ADMET lab software, and the other two conclusion parameters could show active features.

Estimation of toxicity and toxicity classes with Toxtree Software. The toxicity of THCV was analyzed according to Cramer's rules in the in silico study using Toxtree software. The target molecule received a 'Yes' answer only in Question 7.

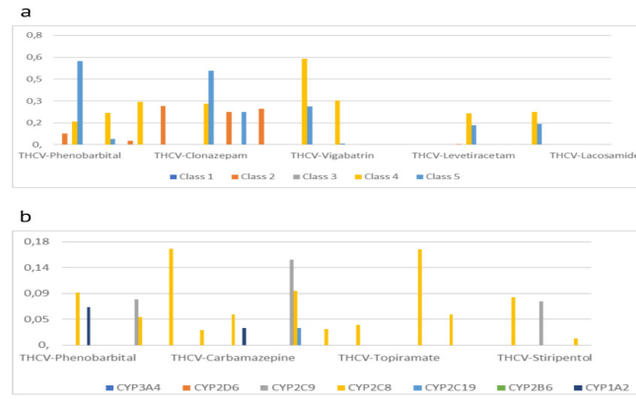

Figure 1. a) Severity classes of drug-drug interactions of THCV with antiepileptic drugs. b) The relationship between THCV's antiepileptic drug groups and drug-drug interactions with P450 enzymes.

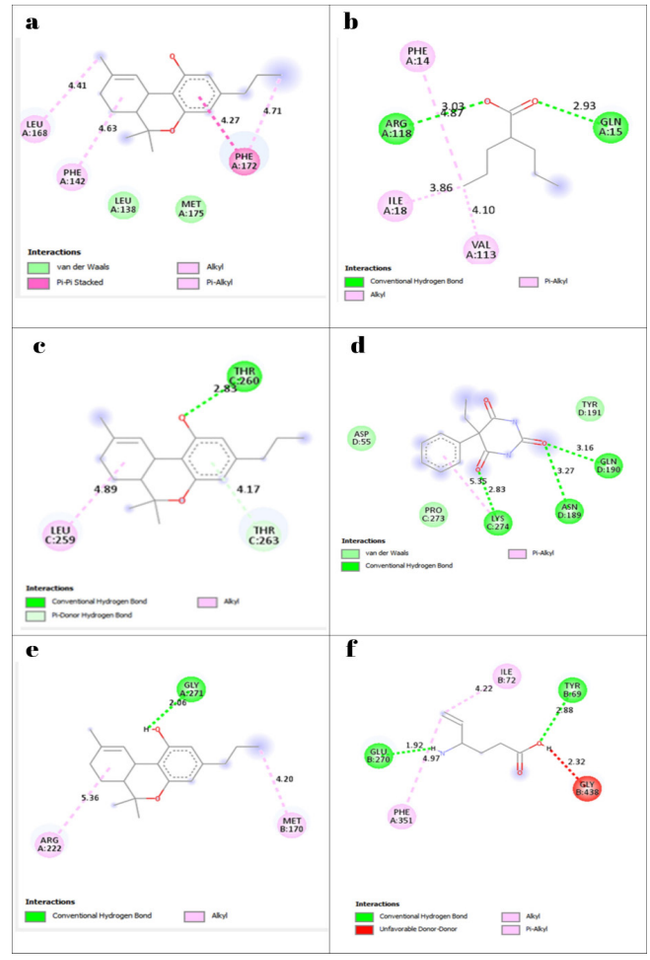

Figure 2. a) protein structure with co-crystallized ligand (PDB ID: 5HVX) b) Position of crystallized ligand within the NAVS binding pocket c) THCV and protein interaction with LigPlot d) THCV and protein interaction with discovery studio e) Protein structure with co-crystallized ligand (PDB ID: 6X3W) f) Position of the crystallized ligand within the GABA A binding pocket, g) THCV and protein interaction with LigPlot h) THCV and protein interaction with discovery studio i) Protein structure with co-crystallized ligand (PDB ID: 1OHW) j) Position of the crystallized ligand within the GABA AT binding pocket k) THCV and protein interaction with LigPlot l) THCV and protein interaction with discovery studio.

Determination of Drug-Drug Interactions using Way2Drug Software. Drug interactions of THCV are shown in Figure 1-a, where Classes 2, 4, and 5 are phenobarbital and levetiracetam; Barbexaclone (Levopropylhexedrine), clonazepam, valproic Grades 4 and 5 with acid, vigabatrin, pregabalin; Class 2 with ethosuximide and oxcarbazepine; Class 2 and 4 with Phenytoin; Carbamazepine in Grades 2 and 5 severity classes. There is no case of interaction with other antiepileptic drugs (Figure 1-a). Interaction of THCV with ethosuximide, clonazepam, vigabatrin, lamotrigine, gabapentin, levetiracetam, pregabalin, and lacosamide was obtained through CYP2C8, whereas CYP2C8 and CYP1A2 interactions with phenobarbital and carbamazepine, CYP2C8 and CYP2C9 interaction with phenytoin, CYP2C8, CYP2C9, and CYP2C19 interaction with valproic acid were obtained. Figure 1-b shows THCV's antiepileptic drug groups and drug-drug interactions with P450 enzymes. Barbexaclone (Levopropylhexedrine), oxcarbazepine, topiramate and zonisamide do not interact via P450 enzymes. The molecular-docking study of the inhibition of Voltage-gated sodium channels, (VGSCs/NavMs) by THCV, the molecular-docking study of the inhibition of GABA A receptor by THCV, the molecular-docking study of the inhibition of GABA - transaminase (AT) receptor by THCV are shown in Figures 2 and 3.

Table 1. Pharmacokinetic properties of THVC using the SwissADME web server

Properties	Parameters	THCV
Physicochemical Properties	Formula	C19H26O2
	MW	286.41 g/mol
	num. H bond acceptors	2
	num. H bond donors	one
Lipophilicity	(implicit log P) iLOPG	3.99
	(P/ w log) XLOGP3	5.89
	MLOGP	3.94
Water Solubility	Log S (ESOL)	-5.41
	Class	Moderately soluble
Pharmacokinetics	GI	High
	BBB	Yes
	LogKp	- 3.87 cm/s
	p- gp substrate	No.
	CYP1A2 inhibitor	No.
	CYP2C19 inhibitor	Yes
	CYP2C9 inhibitor	Yes
	CYP2D6 inhibitor	Yes
	CYP3A4 inhibitor	No.
Drug likeness	Lipinski	yes; 0 violations

Table 3. Ligand molecules with binding scores, hydrogen interactions, and hydrophobic interactions

Compounds	Binding energy (Kcal/mole)	Hydrogen interactions	Hydrophobic interactions
Δ⁹-Tetrahydrocannabivarin	-7.5	-	Leu168(4.41Å), Phe172(4.27Å,4.71Å), Phe142(4.63 Å)
Valproic acid	-5.1	Arg118(3.03Å), Gln15(2.93 Å)	Phe14(4.87 Å) , Val113(4.10 Å), with 18(3.86 Å)
Δ⁹-Tetrahydrocannabivarin	-7.4	Thr260(2.83 Å), Thr263(4.17 Å)	Leu259 (4.89 Å)
Phenobarbital	-7.3	Lys274(2.83 Å), Asn189(3.27 Å), Gln190(3.16 Å)	Lys274(5.74 Å)
Δ⁹-Tetrahydrocannabivarin	-6.4	Glu271(2.06 Å)	Arg222(5.36 Å), Met170(4.20 Å)
Vigabatrin	-4.7	Glu270(1.92 Å), Tyr69(2.88 Å)	Phe351(4.97 Å), with72(4.22 Å)

Table 2. Toxicity model report for THCV and comparison of THCV's Tox21 pathways causing toxicity in Protox and ADMET Lab 2.0 software

Classification	Target	Shorthand	Prediction	Probability	ADMET Lab
Organ toxicity	hepatotoxicity	language	Inactive	0.85	
Toxicity end points	Carcinogenicity	carcinoma	Inactive	0.84	
	Immunotoxicity	immuno	Active	0.95	
	Mutagenicity	mutagen	Inactive	0.74	
	Cytotoxicity	cyto	Inactive	0.83	
Tox21-Nuclear receptor signaling pathways	AhR	nr _ahr	Active	0.82	++
	AR	nr _har	Inactive	0.98	---
	AR-LBD	nr _ar_lbd	Inactive	0.98	---
	Aromatase	nr _aromatase	Active	0.91	++
	ER	nr evil	Inactive	0.84	--
	ER-LBD	nr _er_lbd	Inactive	0.96	-
	PPAR-Gamma	nr _ppar_gamma	Inactive	0.96	++
Tox21-Stress response pathways	nrf 2/ARE	sr _area	Inactive	0.81	+
	HSE	sr _hse	Inactive	0.81	--
	MMP	sr _mmp	Active	0.94	+++
	Tumor suppressor p53	sr _p53	Inactive	0.89	+
	ATAD5	sr _atad5	Inactive	0.96	---

0-0.1(---), 0.1-0.3(--), 0.3-0.5(-), 0.5-0.7(+), 0.7-0.9(++), and 0.9-1.0(+++).

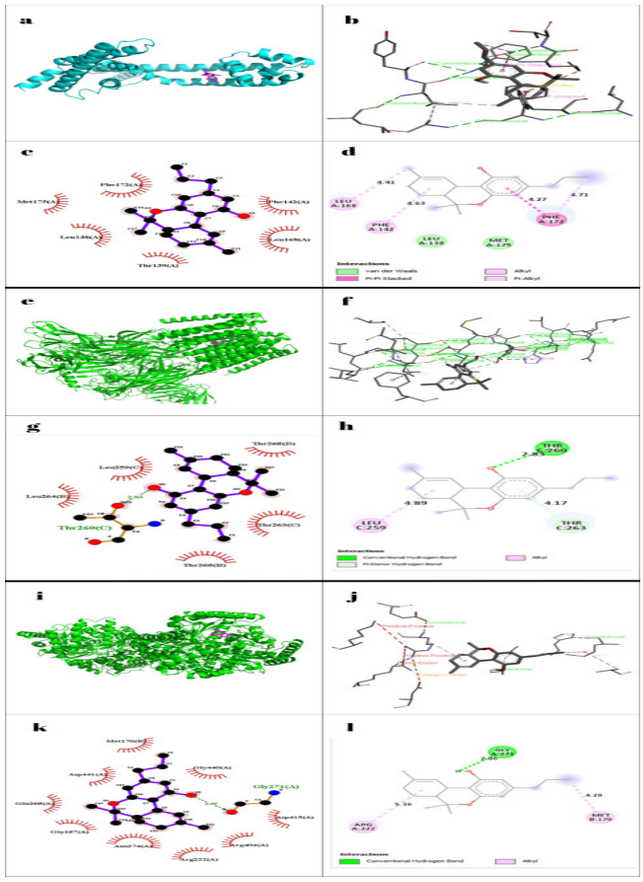

Figure 3. a) NavMs with Δ⁹-Tetrahydrocannabivarin (THCV) interaction b) NavMs with Valproic acid interaction c) GABA A with Δ⁹-Tetrahydrocannabivarin (THCV) interaction d) GABA A with phenobarbital interaction e) GABA AT with Δ⁹-Tetrahydrocannabivarin (THCV) interaction f) GABA AT with Vigabatrin interaction.

Discussion

In this study, the pharmacological properties, drug-drug interactions, and toxicity of THCV were studied and shown in tables in the results section. According to the results of molecular docking studies, we can mention the inhibition of voltage-gated sodium channels (VGSCs/NavMs), inhibition of GABA A receptor, and inhibition of GABA - transaminase (AT) receptor by THCV.

Toxicity Prediction

The pharmacokinetic properties of THVC were examined using the SwissADME web server. It was determined that THCV did not violate any Lipinski rules and passed through the blood-brain barrier. Due to these properties, it has been observed that it may be a suitable candidate for use as a drug. According to the in silico toxicity evaluation, it was determined that the THCV molecule belonged to toxicity class IV and did not show high toxicity to the human body. THCV was evaluated for its hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity properties and was found to have only an immunotoxic effect. Therefore, its immunotoxic effect needs to be investigated with in vitro experiments.

Molecular-Docking study of the Inhibition of Voltage-gated sodium channels (VGSCs/NavMs) by THCV. The target site for ligands of the NavMs protein is found in hydrophobic pockets between subunits running perpendicular to the channel. This appearance of the protein has been termed “fenestrations” and is located in the transmembrane region just below the level of the selectivity filter. NavMs have specific sites for entry of hydrophobic drugs [21,22]. As shown in Figure 2 a-d, THCV molecule NavMs were inserted into the target protein. Compared to valproic acid used as a control, NavMs showed binding affinity with the target protein of -7.5 Kcal/mole, representing a better binding affinity than valproic acid with -5.1 Kcal/mole.

However, valproic acid made hydrogen bonds with Arg118 and Gln15, but no hydrogen bonding was observed in the THCV molecule. The interactions between THCV and the NavM target protein are shown in Figure 3 a-b. THCV molecule showed hydrophobic interactions with Leu168(4.41Å), Phe172(4.27 Å,4.71Å), Phe142(4.63 Å). In the docking study with NavMs, the hydrogen bond formed with the M175 residue, which is known to be specific in the active region of the receptor, is seen as an important amino acid in terms of binding specificity. When the interactions between THCV and NavMs target protein were examined, hydrogen interactions, which is an important interaction in drug interactions, were not observed. At the same time, the fact that its affinity value is higher than that of valproic acid is proof that it can be a drug candidate.

Molecular-Docking study of the Inhibition of GABA A receptor by THCV. The GABA A receptor has several binding sites. For the α1β2α1γ2β2-type pentamer as studied here, there are four sites for Diazepam and two sites for the phenobarbital binding site [23,24]. For comparison, the target ligand was placed at the phenobarbital binding site. The region where the THCV molecule binds to the GABA A receptor is shown in Figure 2 e-h. The insertion result showed a very close affinity with phenobarbital. THCV showed a binding affinity of - 7.4 Kcal/mole, and phenobarbital -7.3 Kcal/mole. The interactions of the THCV molecule and phenobarbital used as Control with GABA A receptor are shown in Figure 3 c-d. A strong 2.83 Å hydrogen bond is established between the carboxyl-bound oxygen atom of THCV and the oxygen atom of the Thr260 amino acid, with Leu259 of 4.89 Å. a hydrophobic alkyl interaction, a 4.17 Å donor with Thr263. It is seen that hydrogen bond is formed with phenobarbital Lys 274 (2.83 Å) and Asn189 (3.27 Å). There were strong hydrogen bonds with Gln190 (3.16 Å). The strongest interaction of THCV with the target protein was a 2.83 Å hydrogen bond between the carboxyl-bound oxygen atom and the oxygen atom of Thr260 amino acid, while Thr263 and a 4.17 Å donor the hydrogen bond is also very important. Compared with phenobarbital, it shows strong hydrogen interactions and better binding energy, making it a suitable inhibitor candidate for the GABA A target protein.

Molecular-Docking study of the Inhibition of GABA - transaminase (AT) receptor by THCV. The THCV ligand was inserted into the binding site for the GABA AT receptor According to the docking result, vigabatrin had an affinity with the GABA AT receptor of -4.7 Kcal/ mole, while THCV showed a higher affinity than vigabatrin with -6.4 Kcal/mole. The interactions of the THCV molecule used as a control and vigabatrin with the GABA AT receptor are shown in Figure 3 e-f. The THCV molecule

formed a strong 2.06 Å hydrogen bond with the carboxyl oxygen attached to the benzene ring and the oxygen atom of the amino acid Gly271. In addition, Arg222(5.36 Å) formed hydrophobic alkyl bonds with Met170 (4.20 Å). In the interaction of Vigabatrin with the GABA AT receptor, Glu270(1.92 Å) and Tyr69(2.88 Å) and hydrogen, Phe351(4.97 Å) and Ile72(4.22 Å) hydrophobic interactions were observed. In the docking study, vigabatrin showed stronger hydrogen interaction with Glu270(1.92 Å) and Tyr69(2.88 Å) than the THCV molecule in its interaction with the GABA AT receptor. In addition, vigabatrin and THCV showed similar hydrophobic interactions. The fact that drugs such as vigabatrin are seen as stabilizing [25] π - π interactions between the Phe351 amino acid and the GABA AT receptor indicates that they were placed in the right spot. The lack of interaction of the THCV molecule with Phe351 suggests that it was located in a different area of the target protein and shows that it localizes to this area with a higher affinity than vigabatrin.

Conclusion

Considering the results of our study, the pharmacokinetic properties of Δ⁹-Tetrahydrocannabivarin are good for absorption, distribution, and liphocity. It was also seen that THCV has low toxicity, conforms to Lipinski's rules, and good binding energy, and with these properties, it could be a therapeutic candidate for epilepsy.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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